Myopericarditis and Enhanced Dystrophic Cardiac Calcification in Murine Cytomegalovirus Infection

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In mice inoculated with murine cytomegalovirus (MCMV) an acute myopericarditis developed which varied from a focal lymphohistiocytic inflammation to intense inflammation with necrosis and cytomegalic inclusion-bearing cells. Sublethal doses caused focal transient nonspecific chronic inflammation, followed months later by an increased frequency and extent of dystrophic cardiac calcification. When such latently infected hearts were heterotopically transplanted into uninfected animals which were then immunosuppressed (IS), a fatal generalized CMV infection followed. Cytomegalic inclusion-bearing endothelial, fibroblastic, and myocardial cells were seen in the intense inflammation found in hearts taken from mice 4 days after lethal inoculation and transplanted into uninfected mice, which were then IS. These findings may be relevant to human cardiac transplantation because they show that MCMV regularly causes cardiac infection with both acute and chronic consequences; chronic injury may follow a morphologically nonspecific myopericarditis which might not be attributed to CMV infection. (Am J Pathol 1986, 124:207–215)

ALTHOUGH human cytomegalovirus (CMV) infection is ubiquitous among organ transplant recipients, including cardiac transplant recipients,[1,2] its effects on the hearts of such individuals have not been defined. In human beings, CMV myocarditis has been described,[3,4] typical cytomegalic cells with intranuclear inclusions have been observed in the hearts of infants with generalized CMV disease,[5] and CMV-infected myocardial cells have been detected in generalized infection.[6] In the mouse, both acute and latent cardiac infection with murine CMV (MCMV) has been described,[7] and a focal myocarditis has been observed,[8] but the long-term effects of such infection on the heart are currently undefined. Other viruses can cause myopericarditis in human beings[9,10] and in mice,[11] and in both the inflammatory process can be prolonged and the cardiac injury may be accompanied by dystrophic cardiac calcification (DCC)[11–16] and heart failure.[14,17] DCC also occurs in certain strains of mice, including BALB/c, in the absence of infection[18]; it is apparently due to an autosomal recessive inheritance[19]; and age, diet, sex, and parity[20] are among its predisposing factors. However, to our knowledge, it has not been reported in association with CMV or MCMV infection.

In this paper we report our observations on the effect

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of MCMV infection on the heart. Acute or latent, lethal and sublethal infections with and without immunosuppression were studied in a murine cardiac transplantation model which employed unmated adult female BALB/c mice. The results showed that MCMV causes a myopericarditis which can be focal, nonspecific, and transient, or extensive and pathognomonic. Moreover, this transient process augments the predisposition of BALB/c mice to DCC. The observations may have relevance for human cardiac transplantation because cardiac pathology (DCC) can develop after apparently nonspecific and transient inflammation induced by cytomegalovirus.

Materials and Methods

Virus

Virulent Smith strain MCMV is maintained in this laboratory by serial passage in CD-1 Swiss mice (obtained from Charles River Breeding Laboratory, Wilmington, Mass). The virus stocks consist of 10% (wt/vol) homogenates of salivary glands harvested 3 weeks after the intraperitoneal injection of 10^3 plaque-forming units (PFU) into 21-day-old mice. The homogenates are prepared in Dulbecco's medium supplemented with 10% fetal calf serum and 10% dimethyl sulfoxide. Control inoculations utilized uninfected salivary gland homogenates (NSG) prepared in a similar fashion from weanling mice inoculated with saline. Both the virus and the NSG control suspension are stored until used at −70 C.[6] The virus stocks have a titer of 10^8 PFU/ml.

Animals

All mice were unmated adult female BALB/c mice purchased from Cumberland View Farm (Clinton, TN). In these experiments all mice were housed in polycarbonate cages with bonnets, no more than 6 per cage, and fed Purina Laboratory Chow (11% fat) and water *ad libitum*.

Infections

Acute lethal infections were produced by the inoculation of $10^{5.5}$ PFU of MCMV intraperitoneally which regularly produced death 6–7 days later. Latent infections were produced by the intraperitoneal inoculation of 10^4 PFU of MCMV, a sublethal dose. Control animals were inoculated intraperitoneally with an equal volume of NSG. All mice were then maintained in our animal facility for 4–6 months in cages with bonnets for prevention of cross-infection. At that time, months after MCMV inoculation, mice were shown to have an antibody titer of $\geq 1{:}128$ by indirect immunofluorescence assay and to have no detectable virus on plaque assay of their salivary glands and other viscera; that is to say, they were latently infected. Control mice, mice which had been inoculated months earlier with NSG, were shown to have an antibody titer of $<1{:}16$; and virus was never recovered from their salivary glands.[7]

Transplantation

Primary, vascularized heterotopic cardiac transplantation was carried out as previously described.[7] Briefly, the aorta and pulmonary artery of the heart to be transplanted were joined end-to-side to the recipient abdominal aorta and inferior vena cava under chloral hydrate anesthesia and ×25 magnification. Back blood flow into the coronary vessels of the transplanted heart was followed by sinus rhythm. The abdominal incision was closed, and the animal was allowed to recover under a heat lamp for a few hours, after which it was returned to its cage.

Immunosuppression

For experiments in which immunosuppression (IS) was employed, cortisone acetate (Merck, Sharpe and Dohme Div., Merck & Co., West Point, NY) 125 mg/kg/day, and 0.2 ml of rabbit antimouse thymocyte serum (ATS) (kindly supplied by Henry Winn, Ph.D., Transplantation Unit, Massachusetts General Hospital, Boston, Mass) twice weekly, were both administered intraperitoneally. Control mice were given injections of equivalent volumes of phosphate-buffered saline (PBS) according to the same time schedule.

Gross Pathology and Histologic Studies

At varying intervals after inoculation or transplantation animals were killed by cervical dislocation, and the transplanted heart, recipient heart, and other recipient organs were removed and examined grossly for evidence of dystrophic calcification. All tissues were placed in 10% formalin and submitted for histologic examination. Sections made from the hearts and other organs were stained with hematoxylin and eosin (H&E). Samples were code-labeled so that the reviewing pathologist would not know whether the heart had been infected or whether the mouse had been treated with IS. All heart sections were examined for the nature and amount of calcification and inflammation and for the presence of viral intranuclear inclusion bodies. In the initial set of observations, those concerning the frequency and extent of macroscopically evident pericardial calcification (DCC) in latently infected mice,

its extent was scored as 1+ (mild), 2+ (moderate), and 3+ (extensive). In all subsequent experiments a scale of 1+ to 4+ was used for grading microscopic calcification. A heart with 4+ calcification was that characterized by circumferential or near-circumferential visceral pericardial and outer myocardial calcium deposition, whereas a heart with 1+ calcification contained one to three scattered pericardial plaques. A heart with 2+ calcification was characterized by multiple discrete foci of myocardial and pericardial calcification, and a heart with 3+ calcification was characterized by large, confluent pericardial and outer myocardial plaques involving half the circumference of individual heart sections. Lymphohistiocytic inflammation was graded from trace (tr), indicating scattered cells, to 4+, which indicated extensive diffuse infiltration. Neutrophilic infiltration was excluded from this grading because it was presumed to be in response to ischemic necrosis in most cases. In some instances, the other organs of the transplant recipient (including liver, spleen, salivary glands in all animals and lymph nodes, pancreas, adrenals, and lungs in some animals) were similarly examined for calcification, inflammation, and inclusion bodies.

Virus Assay

The quantity of virus present in a tissue was determined by plaque assay on secondary mouse embryo cell culture overlaid with tragacanth, as described previously.[7]

Experimental Design

Determination of Whether Sublethal MCMV Infections Induce Acute Myopericarditis

Nine 5-week-old unmated female BALB/c mice were divided into two groups; 5 were inoculated with 10^4 PFU MCMV and 4 with NSG. All were caged and fed in the same way. On the fifth day after inoculation, all were sacrificed, and their hearts were examined histologically and virologically.

Determination of Effect of Sublethal, Latent, MCMV Infection on DCC

Thirty-five 5-week-old unmated female BALB/c mice were divided into two groups. Twenty were inoculated intraperitoneally with 10^4 PFU MCMV, and 15 were inoculated intraperitoneally with NSG. All were fed the same food and water *ad libitum*. Four to 5 months later at the time the hearts were being removed for heterotopic cardiac transplantation, each heart was examined for the presence and extent of external DCC visible to the unaided eye as opaque white plaques on the surface of the right ventricle. In this one instance (chronologically the first observations made), the DCC was graded as absent, 1+ (minimal), 2+ (moderate), or 3+ (extensive).

In a companion, subsequent experiment, the hearts of 10 7-month-old unmated female BALB/c mice, which had been inoculated 6 months earlier, 5 with MCMV and 5 with NSG, were examined microscopically for DCC.

Effect of MCMV on DCC in Donor and Recipient Hearts After Heterotopic Cardiac Transplantation With and Without Immunosuppression

Thirty-eight unmated adult female BALB/c mice received heterotopically transplanted hearts. Of these recipients, 12 had been latently infected by the inoculation of 10^4 PFU MCMV intraperitoneally 4–6 months earlier; 26 had not been inoculated. The 12 latently infected recipient mice received hearts from mice which 4–6 months earlier had been inoculated with NSG. Thirteen of the uninoculated (uninfected) recipient mice received latently infected hearts, that is, hearts from mice which had been inoculated 4–6 months earlier with 10^4 PFU MCMV intraperitoneally. A comparison was made between uninfected and infected hearts obtained when the mice were sacrificed 1–4 weeks after transplantation. There was no significant difference in time of harvest between the uninfected and infected hearts.

For purposes of this analysis, a heart was considered to be infected if that heart was the transplanted heart obtained from a latently infected mouse, or the recipient heart of a latently infected mouse (regardless of the recipient's immunosuppressive treatment). In contrast, a heart was considered to be uninfected if the mouse source of the transplanted heart and the recipient mouse had never been inoculated with MCMV (ie, neither was latently infected), regardless of whether immunosuppressive treatment had been administered. We did not include in this analysis either those initially uninfected transplanted or recipient hearts which might have become infected as a result of immunosuppression, or their potential controls, that is, initially uninfected hearts, whether they had been transplanted or were those of recipient mice which had not received IS.

Effect of Lethal Infection, Transplantation, and IS

In these experiments adult female BALB/c mice were inoculated with $10^{5.5}$ PFU, a lethal dose; and 4 days later their hearts were removed and heterotopically transplanted into uninfected mice of the same age, sex, mating status, and strain. Control animals differed only in that they were inoculated with NSG. Hearts were removed and examined 3–14 days after IS had been started (4–15 days after transplantation).

Table 1—Microscopic DCC and Inflammation in Acute and Latent MCMV Infection

Acute sublethal infection		Latent infection	
Infected	Control	Infected	Control
0/3+ *	1+/tr	2+/tr	1+/tr
0/2+	0/tr	3+/tr	1+/0
1+/4+	0/tr	1+/tr	0/0
0/tr	0/tr	2+/tr	0/0
0/4+	ND†	3+/tr	1+/0

* Calcification/inflamation (microscopic). Each such entry is that for 1 mouse.

† Not done.

Results

Acute Cardiac Infection and Myopericarditis Induced by Inoculation of Sublethal Dose of MCMV

Five days after intraperitoneal inoculation of a sublethal dose of virus the average concentration of MCMV in the hearts of 4 mice was $10^{2.5}$ PFU/g (all contained virus); virus was not detected in either of the hearts of two mice inoculated with NSG (the hearts of 1 infected and 2 uninfected mice were not examined virologically).

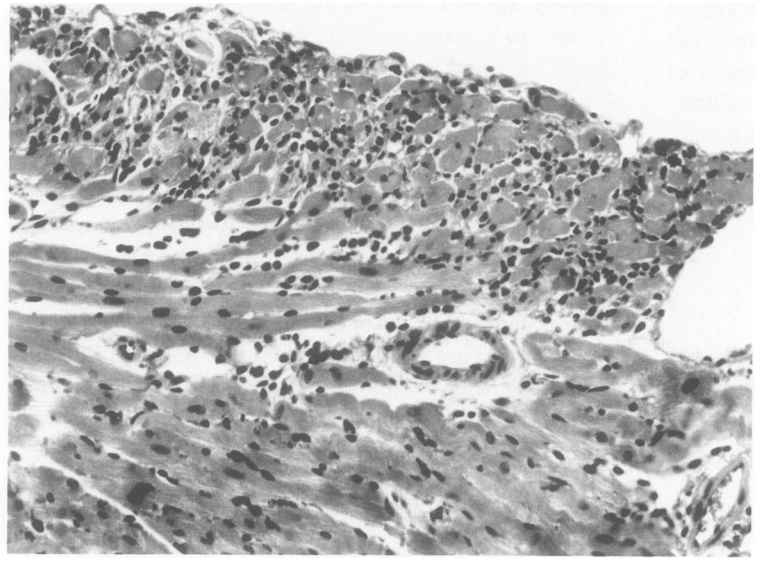


Figure 1—Prominent lymphoid infiltrate associated with coagulation necrosis of myocardial fibers in the outer myocardium and pericardium of a mouse 5 days after inoculation with a sublethal dose of MCMV. (H&E, ×85)

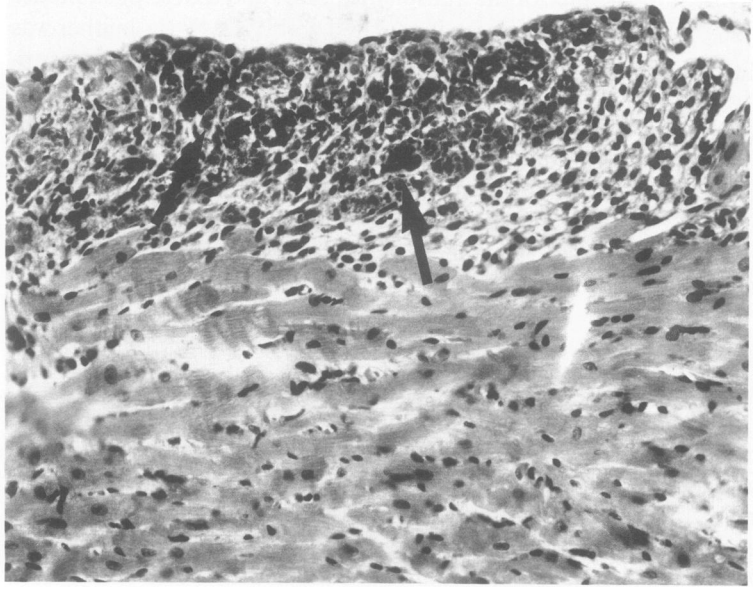


Figure 2—Early dystrophic calcification of necrotic myocardial fibers in the heart of a mouse inoculated with a sublethal dose of MCMV 5 days earlier (*arrows*). (H&E, ×85)

Table 2—External Macroscopic DCC in Latent MCMV Infection

Degree of calcification	Mice	
	Latently infected	Control
3+	13/20 (65%)	0/15 (0%)
2+	2/20 (10%)	1/15 (7%)
1+	2/20 (10%)	5/15 (33%)
None	3/20 (15%)	9/15 (60%)
Total with calcification	17/20 (85%)	6/15 (40%)

Mice acutely infected with a sublethal dose of MCMV and sacrificed 5 days later exhibited patchy outer myocardial and pericardial inflammation and necrosis (Table 1, first column; and Figure 1). The heart of one mouse in the acutely infected group demonstrated early calcification of necrotic myocardial fibers associated with the infection (Figure 2). The hearts of NSG inoculated animals sacrificed at 5 days did not show evidence of myocarditis or calcification with the exception of a single mouse which had 1+ calcification.

DCC in Latent MCMV Infection

Sixty-five percent of the 20 hearts from latently infected mice, mice which had been inoculated with a sublethal dose of MCMV 4–6 months previously, had extensive (3+) macroscopic calcification visible over the surface of the right ventricle. Only 15% had none (Table 2). In contrast, 60% of the hearts from uninfected mice had no externally evident calcification, and none had 3+ calcification ($P < 0.05$).

Microscopically, there were scattered pericardial plaques (1+ to 2+ DCC); 2 mice had 3+ DCC in a pericardial–outer myocardial pattern, and there was obvious replacement of myocardial fibers by calcium plaques (Table 1, second column). While focal aggregates of chronic inflammatory cells were found surrounding some of the calcium deposits, elsewhere there was no evidence for myocarditis, nor were intranuclear inclusions found. Virus was not recovered on direct plaque assay of the heart.

Effect of MCMV on DCC After Heterotopic Transplantation

The results found in the hearts of animals sacrificed after transplantation (Table 3) were like those observed in the hearts of latently infected mice examined prior to transplantation. Of 25 infected hearts as defined in the third section under Experimental Design in Materials and Methods, 22 (88%) had dystrophic calcification of the visceral pericardium and outer myocardium. Only 8 (31%) of the 26 uninfected hearts had dystrophic calcification ($P < 0.01$) (Table 3).

Calcium deposits for the most part were located in the visceral pericardium (epicardium) and peripheral myocardium and took the form of large concretions (Figures 3 and 4). In the hearts of latently infected mice, calcium deposition tended to involve both the pericardium and underlying myocardium with evidence of myocardial fiber replacement, while in uninfected groups the pattern was primarily that of pericardial calcification. DCC was more frequently found in those uninfected hearts that had been subjected to transplantation and IS (6/8) than in those which had been subjected to neither (0/5) (Table 3). IS *per se* did not appear to affect the distribution of calcification. Occasionally extensive calcification was noted in areas of necrosis both in infected animals and controls; necrosis could be associated with having transplanted the heart and was assumed to be secondary to ischemia.

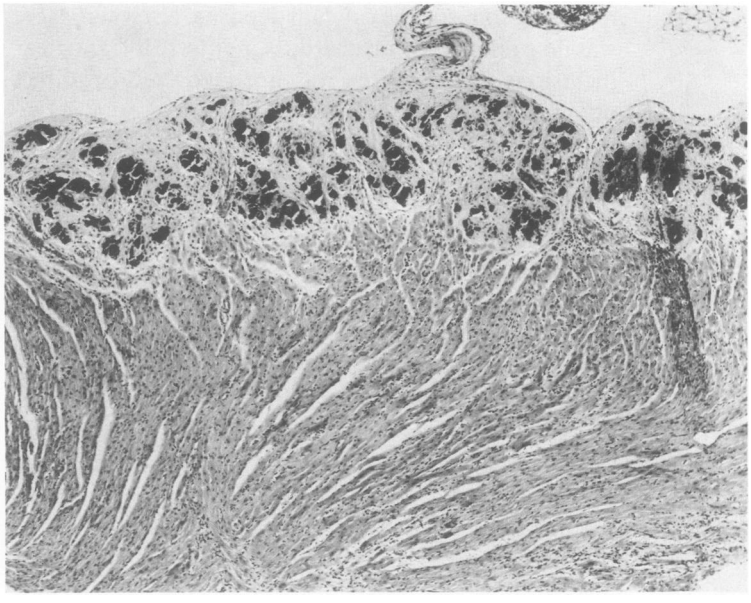
Neither calcification nor atherosclerotic changes were observed in coronary arteries.

Inclusion bodies, inflammation, and calcification were not found in the liver, spleen, salivary glands, or

Table 3—Microscopic DCC in MCMV Infection After Transplantation

Examined Heart	Recipient CMV status	Conor CMV status	Treatment	No. with calcification/ no. examined	Total no. with calcification/ total no. examined
Infected group					
Recipient	LI	U	IS	7/7	
Recipient	LI	U	PBS	4/5	
Transplanted	U	LI	IS	5/6	
Transplanted	U	LI	PBS	6/7	22/25 (88%)
Uninfected group					
Recipient	U	U	IS	1/8	
Recipient	U	U	PBS	0/5	
Transplanted	U	U	IS	6/8	
Transplanted	U	U	PBS	1/5	8/26 (31%)

LI, latently infected, U, uninfected.



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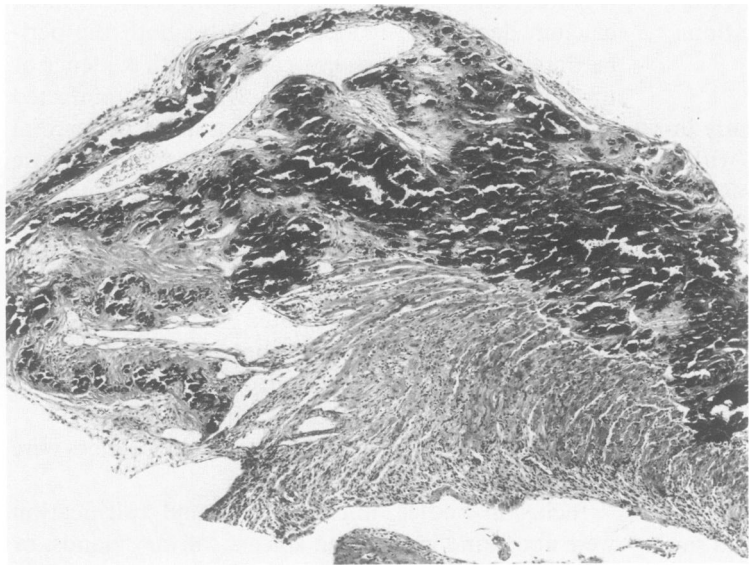

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Figure 3—Pericardial and outer myocardial calcification (2+) in a latently infected transplanted heart removed 2 weeks after transplantation from a recipient that received no IS. (H&E, ×50) **Figure 4**—Pericardial myocardial calcification (4+) in latently infected transplanted heart removed 2 weeks after transplantation from a recipient that received IS. (H&E, ×50)

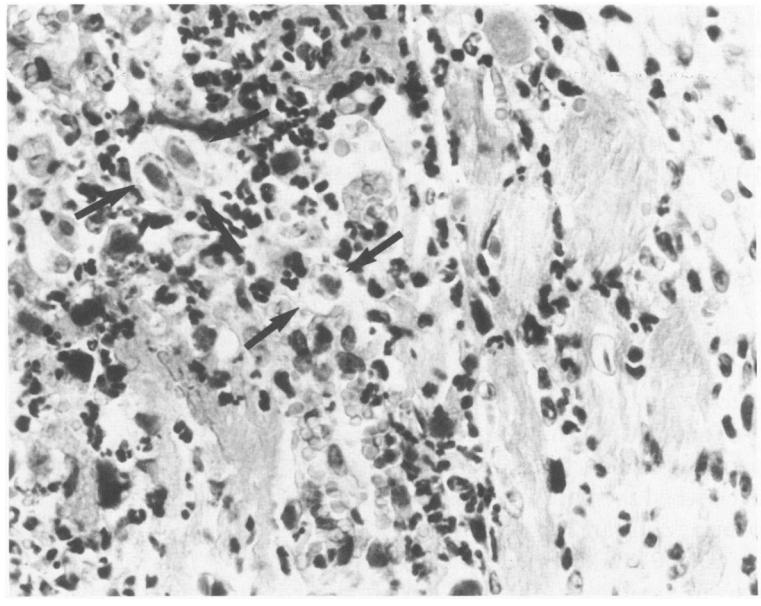
adrenals of latently infected animals after transplantation.

Effects of Lethal Infection, Transplantation, and IS

Hearts which had been taken from lethally infected donors and transplanted into mice which then received IS had intense inflammation with necrotic myocytes and typical inclusion-bearing cytomegalic cells (Figure 5). Enlarged endothelial cells, fibroblasts, and myocardial cells were found which contained typical intranuclear inclusions. Typical cytomegalic changes were found in the adrenals, livers, salivary glands, and spleens of these recipient mice, but not in their (recipient) hearts. Calcium deposition was not seen in hearts transplanted from lethally infected mice, nor in the hearts or other organs of previously uninfected recipient mice. All transplanted hearts had some areas of ischemic necrosis, probably due in part to the ischemia associated with the transplantation process. In hearts which had been taken from lethally infected donors and transplanted into recipients which then did not receive IS, a multifocal interstitial lymphohistiocytic infiltrate was present in well-preserved areas (Figure 6). Typical MCMV cytomegalic inclusions were not seen in those hearts.

Discussion

These observations establish that MCMV induces a myopericarditis in association with its infecting the heart during lethal and sublethal infections, and that



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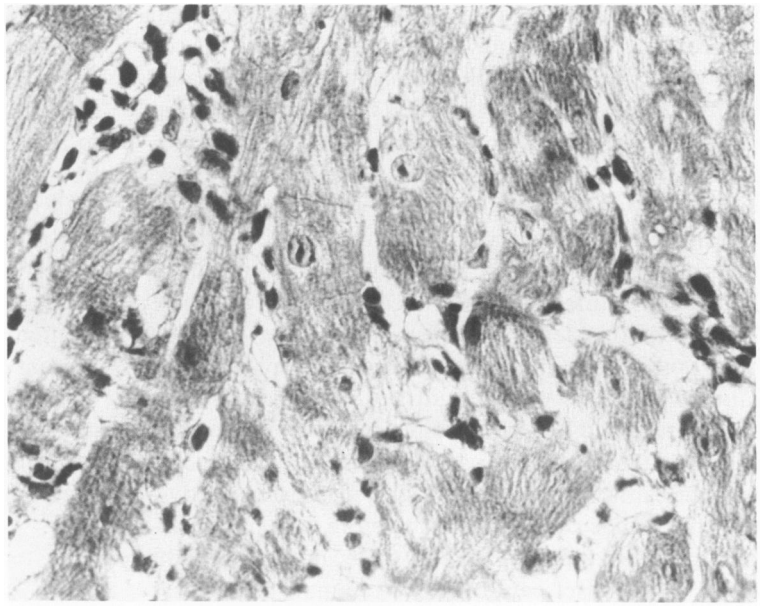

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Figure 5—Extensive acute and chronic inflammation associated with typical cytomegalia and intranuclear inclusions (*arrows*) in a heart transplanted from a lethally infected donor, removed 9 days after transplantation from recipient that received IS. (H&E, ×500) **Figure 6**—Patchy lymphohistiocytic interstitial infiltrate without cytomegalic inclusions in a heart transplanted from a lethally infected donor, removed 9 days after transplantation from a recipient that received no IS. (H&E, ×500)

MCMV infection augments the predisposition of BALB/c mice to DCC. In the current studies, $10^{2.5}$ PFU MCMV/g cardiac tissue were recovered 5 days after intraperitoneal inoculation of 10^4 PFU, a sublethal dose. The extent of MCMV multiplication in the heart was first noted in the initial report of this series[7]; $10^{4.5}$ PFU MCMV/g heart was recovered 7–8 days after inoculation of a lethal quantity of virus (and 3 days after the acutely infected heart was transplanted into an otherwise uninfected recipient, which was then given IS). Hearts of recipient mice uninfected until receiving transplanted infected hearts and 14 days of immunosuppressive treatment contained 10^4 PFU/g. Others have reported neither the recovery from nor the extent of multiplication in the heart. Papadimitriou et al found foci of necrosis, mononuclear and polymorphonuclear cells, and some cardiac myocytes with typical MCMV inclusions in beige mutants of C57BL/6 mice during lethal infections, but the quantity of virus was not determined.[8] Shanley et al,[21] using C3H mice and the same methods of inducing latency and reactivation with immunosuppresives as we, did not observe MCMV lesions in the myocardium; no data were given to indicate whether MCMV was recovered from the heart. The observations here reported show that MCMV infection of the heart induces a range of inflammatory changes ranging from focal lymphohistiocytic inflammation to intense diffuse necrotic inflammation associated with

inclusion-bearing cytomegalic myocytes, fibroblasts, and endothelial cells. There was a direct correlation between the severity of inflammatory response and the extent of viral multiplication; $10^{2.5}$ PFU/g were recovered from hearts with focal inflammation, and $\geq 10^4$ PFU/g from hearts with intense inflammation and necrosis.[7] The degree of inflammation and necrosis was also influenced by whether the heart had been transplanted and whether IS was administered.

As stated, MCMV was not recovered from latently infected hearts by direct plaque assay, but in earlier studies the latent MCMV was activated and recovered after cell and explant cultures of such hearts.[22]

Human CMV may infect cardiac myocytes during generalized infections in immunodeficient individuals even when the pathognomonic cytomegalic inclusion-bearing cells are not detected, as found by Myerson et al, using CMV specific *in situ* DNA hybridization.[6] This may be analogous to the MCMV situation in sublethal infection. Human CMV occasionally causes clinical myocarditis[3,4]; Wink and Schmitz reported the case of a 31-year-old male who died of myocarditis associated with an acute CMV infection; CMV inclusions were not found in the heart, although there was a focal lymphocytic infiltration and focal fibrosis.[3] They and other authors, Woodruff[9] and Lerner,[10] have reported and reviewed similar observations, but clinically evident myocarditis as a frequent or regular manifestation of human CMV infection has not been reported, and there have been no systematic surveys for CMV myocarditis or its possible late effects in the human transplant population. Those surveys should be done, because the studies reported here show that a relatively inapparent MCMV infection which causes a transient nonspecific myopericarditis is frequently followed by extensive dystrophic cardiac calcification; therefore, it seems possible that an inapparent human CMV infection might cause a late-onset cardiopathy in human beings.

In mice, Coxsackie B3 and B4 and encephalomyocarditis (EMC) viruses can induce a severe myopericarditis followed by cardiac fibrosis, DCC, and congestive heart failure (CHF),[11-14] and Coxsackie B viruses and Echovirus 11 can cause an acute, sometimes fatal, myopericarditis in man, and these may be associated with DCC.[10,15,16] Matsumori and co-workers developed such a model using DBA/2 mice and EMC; it was characterized by dilation, hypertrophy and DCC of the right ventricle, and CHF.[17]

Calcium deposition in the pericardium and myocardium (DCC) was first demonstrated in the absence of infection and in association with the aging process; it was found especially in the retired breeders of certain strains of mice.[18] Notably involved are C3H and DBA mice; BALB/c and A/J mice are less frequently affected. Brownstein showed that in DBA/2 mice this dystrophic epicardial mineralization was probably determined by several autosomal recessive alleles.[19] Earlier, Eaton et al[20] demonstrated that DCC was augmented by increasing the fat in the diet or administering cortisone, which caused cardiac necrosis; they also showed that females (especially breeders) and certain mouse strains were especially afflicted with DCC.

The frequency of DCC in BALB/c mice without infection varies considerably. Madison et al found calcium deposits on the hearts of 159 (7.6%) of 2088 untreated, unmated male and female BALB/c Cr mice killed when 18 months old.[23] The fat content of the diet was not noted, nor was any difference between the sexes. In a different report 75% of 20 unmated female BALB/c mice killed primarily because of pulmonary tumors had DCC; in none was it extensive.[20] In mated females and males the observed frequency was lower: 24/73 (33%) of females and 20/58 (34%) of males had it; in a few was it extensive. Our findings were similar to these latter observations: 30–40% of the untreated, uninfected mice had DCC. Because the frequency of DCC in the MCMV infected BALB/c mice exceeded 85%, these results establish that MCMV augments the predisposition of BALB/c mice to DCC.

Is the DCC induced by MCMV associated with cardiac dysfunction? Might these data indicate that similar processes could operate in the human being afflicted with CMV infections activated in a transplanted heart by immunosuppression? These are important questions raised by our observations, which establish that MCMV causes a transient, morphologically nonspecific myopericarditis; one that is followed by a cardiac pathology (DCC) that might cause cardiac dysfunction.

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